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Haemodynamic effects of glucagon

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The central and peripheral vascular haemodynamic effects of glucagon were studied in 29 patients. With a single dose method of 2 or 5 mg. glucagon intravenously the inotropic action of the drug produced immediate increased myocardial contractility with significant increase in cardiac output and enhanced cardiac performance, and lowering of pulmonary arterial pressure and pulmonary vascular resistance. No primary peripheral vascular effect was evident, and the increased systemic pressure and lowered systemic resistance appear to be secondary to the central action of the drug. With the dosage used there were no undesirable side-effects apart from a feeling of slight nausea. Though the haemodynamic effects are abrupt, reaching their maximum values in the first 10 minutes after injection, they tend to be dissipated within half an hour, presumably due to the very rapid destruction of the drug. Repeated booster doses rather than continuous infusion may be the method of choice to maintain an increased cardiac output. The positive chronotropic action of the drug may cause transient palpitations. Glucagon increased the cardiac output in the acute phase of myocardial infarction by 42 per cent. The haemodynamic effects in chronic rheumatic heart disease are more varied, and it may increase left atrial pressure in mitral stenosis, which is undesirable. Hyperglycaemia results from liver glycogenolysis but blood sugar levels rarely exceeded 200 mg./100 ml. These results warrant further study of the value of glucagon as a positive inotropic agent in low output heart failure, especially in acute myocardial infarction with cardiogenic shock, or after cardiac surgery, or in unrelieved chronic congestive heart failure.

The pancreatic polypeptide glucagon which is synthesized in the α-cells of the islets of Langerhans has been shown experimentally to have a positive inotropic action on the mammalian heart (Farah and Tuttle, 1960; Regan *et al.*, 1964; Glick *et al.*, 1968; Lucchesi, 1968). More recent investigations have shown a similar action on the human myocardium (Klein, Morch, and Mahon, 1968; Linhart *et al.*, 1968; Williams *et al.*, 1969). The hormone is now available in a relatively pure form (Eli Lilly Inc., Indianapolis), and it appears useful to assess its value as an agent to increase the performance of the heart in clinical practice. Lal and Fletcher (1969) have already suggested its potential use in the acute phase of myocardial infarction to augment the cardiac output. Any drug that improves the circulation without unwanted side-effects would be a valuable adjuvant to the digitalis glycosides and the catecholamines in current use as myocardial stimulants. Accordingly, a project was devised to measure the central and peripheral haemodynamic effects of glucagon in patients with organic heart disease.

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Patients and Methods

A total of 29 patients was studied; they were divided into the following groups: (1) the acute phase of myocardial infarction (8 patients); (2) chronic rheumatic heart disease (11 patients); (3) a selection of 10 patients chosen for measurement of forearm and calf blood flow. As the technique varied for each group the methods and results will be described for each in turn.

Group 1: acute myocardial infarction Two methods of administration were chosen. (a) The single dose method, in which 2 or 5 mg. glucagon were injected directly into the pulmonary artery over a period of one minute, and (b) the continuous infusion method in which 20 mg. glucagon were administered in one litre of 5 per cent dextrose solution every 24 hours for a total of 48 hours. The 8 patients, 7 men and 1 woman, aged 40–73 years, were under treatment in the coronary care unit and agreed to the investigations. The cardiogram confirmed the acute phase of myocardial infarction in all (World Health Organization, 1959), and the observations were made during the 48-hour period after the onset of infarction. No drugs had been administered for at least

8 hours before control readings. A polyethylene catheter (P.E. 60) was inserted percutaneously into an arm vein and allowed to float into the pulmonary artery. The radial artery was cannulated using a 'Medicut' cannula (Brunswick Corporation). Both catheters were kept heparinized and left *in situ* throughout the period of observation. No complications occurred. Pulmonary and systemic arterial pressures were measured using a Consolidated Electrodynamics transducer, the sternal angle being used as the reference point for pressure readings. Cardiac output was determined after injecting 2·5 mg. indocyanine green dye into the pulmonary artery with radial artery withdrawal through a Gilford densitometer. Recordings were made on a Galileo ultraviolet recorder, and electrocardiographic tracings were taken during all the observations. The stroke volume, total pulmonary resistance, and total systemic resistance were calculated, resistance being expressed in dynes/sec./cm.$^{-5}$ Control values were measured before administration of glucagon.

(*a*) *Single dose method*

This method was used in 5 patients. The dose of glucagon injected into the pulmonary artery was 5 mg. in 4 patients, and 2 mg. in 1 patient. Measurements were repeated at intervals of 5, 10, 20, and 30 minutes after completion of the glucagon injection. Blood samples were collected from the radial artery at the time of the control measurements and at the 30-minute interval for blood sugar estimations.

Results of single dose method

The results are summarized in Tables 1 and 2.

Cardiac output (Table 1) There was a striking increase in cardiac output in all the patients. The maximum percentage increase occurred within the first 10 minutes after the injection of glucagon (Case 2, 58% at 5 minutes, and Case 3, 79% at 10 minutes). The over-all percentage increase calculated from the differences of maximum values from control values is 42 per cent. At the 30-minute period the cardiac output remained high in 2 patients (Cases 1 and 5), diminished in 2 (Cases 2 and 3), and unchanged in 1 (Case 4). It will be noted that a dose of 2 mg. glucagon in one patient (Case 5) significantly increased the cardiac output.

Stroke volume (Table 1) The stroke volume was increased in 4 patients (Cases 1, 2, 3, and 5) and accounted for the increased cardiac

TABLE 1 *Group I—acute myocardial infarction: (a) Effects of single injection of glucagon into pulmonary artery on cardiac output, heart rate, and stroke volume*

	Control			*5 min.*				*10 min.*				*20 min.*				*30 min.*			
Case No. (dose mg.)	*CO*	*SV*	*HR*	*CO*	*SV*	*HR*	*CO change (%)*	*CO*	*SV*	*HR*	*CO change (%)*	*CO*	*SV*	*HR*	*CO change (%)*	*CO*	*SV*	*HR*	*CO change (%)*
1 (5)	4·1	55	75	5·3	67	80	+29	4·8	59	82	+17	5·0	67	76	+22	4·5	60	74	+10
2 (5)	2·4	29	82	3·8	33	114	+58	3·0	31	100	+25	—	—	—	—	2·3	26	86	−4
3 (5)	5·3	51	104	5·3	48	112	0	9·5	87	110	+79	4·9	47	106	−8	3·7	36	106	−30
4 (5)	3·0	45	68	3·8	42	90	+26	3·0	43	72	0	3·0	44	70	0	3·0	45	68	0
5 (2)	5·3	62	86	—	—	—	—	6·4	75	86	+21	5·6	67	84	+6	6·0	73	84	+13

CO, cardiac output (l./min.); SV, stroke volume (ml./beat); HR, heart rate (beats/min.).

TABLE 2 *Group I—acute myocardial infarction: (a) Effects of single injection of glucagon into pulmonary artery on pulmonary and systemic mean pressures, and total resistances*

Case No. (dose mg.)	*Control*				*5 min.*				*10 min.*				*20 min.*				*30 min.*			
	$\bar{A}P$	$\bar{PAP}$	*TSR*	*TPR*	*AP*	*PAP*	*TSR*	*TPR*	*AP*	*PAP*	*TSR*	*TPR*	*AP*	*PAP*	*TSR*	*TPR*	*AP*	*PAP*	*TSR*	*TPR*
1 (5)	83	26	1613	502	91	24	1361	360	91	23	1501	387	86	23	1353	357	91	25	1614	454
2 (5)	93	32	3155	1070	98	20	2084	432	92	35	2385	903	—	—	—	—	79	25	2782	902
3 (5)	99	27	1488	401	112	26	1677	382	114	24	960	199	106	25	1720	409	98	15	2083	308
4 (5)	61	19	1586	496	73	23	1377	483	65	18	1698	473	63	17	1628	436	64	15	1698	392
5 (2)	71	20	1066	298	—	—	—	—	75	18	928	228	79	18	1114	248	79	19	1032	253

$\bar{A}P$, mean arterial pressure (mm. Hg); $\bar{PAP}$, mean pulmonary arterial pressure (mm. Hg); TSR, total systemic resistance (dynes/sec./cm.$^{-5}$); TPR, total pulmonary resistance (dynes/sec./cm.$^{-5}$).

output. In 1 patient (Case 4) the stroke volume was not significantly increased, the augmented cardiac output being due to increased heart rate.

Heart rate (Table 1) The sinus rate was increased in the patients who received 5 mg. glucagon, the over-all increase above control values being 17 per cent. In 1 patient (Case 5) who received 2 mg. glucagon only the heart rate was not significantly altered. The sinus rhythm remained undisturbed in all patients.

Mean pulmonary arterial pressure (Table 2) With the exception of 1 patient (Case 4) in whom the mean pulmonary arterial pressure was only slightly raised, there was an average maximum fall of 25 per cent from control values at some point during the 30-minute period of observation.

Total pulmonary vascular resistance (Table 2) The mean pulmonary vascular resistance was significantly lowered in all patients, the percentage fall from control values being 37 per cent at some point during the 30-minute period of observation.

Mean arterial pressure (Table 2) The mean arterial pressure was increased in all patients, the over-all percentage increase being 8 per cent. In one patient (Case 2) it fell by 15 per cent from the control value at the 30-minute interval.

Total systemic resistance (Table 2) With the exception of one patient (Case 3) in whom the total systemic resistance rose by 13 per cent at the 5-minute interval, there was an over-all fall of 19 per cent for the group as a whole.

Blood sugar The control blood sugars were normal (< 100 mg./100 ml.). Glucagon caused hyperglycaemia, but at the 30-minute interval no blood sugar level exceeded 200 mg./100 ml.

Side-effects Each patient noticed a transient feeling of nausea shortly after completion of the glucagon injection. There was no vomiting. There was an associated feeling of warmth, and the patients hands felt warm to the observer.

(*b*) *Continuous infusion method*

Three patients were studied. The parameters were measured at 24 and 48 hours after the control values were obtained.

Results of continuous infusion

The results are shown in Table 3. In the first patient (Case 6) there was an episode of atrial fibrillation at 24 hours, which accounts for the lowered cardiac output from 3 l./min. to 2·46 l./min. At 48 hours the cardiac output was increased by 16·6 per cent due to increased stroke volume as the restored sinus rate was not significantly changed from the control recording. There was little change in systemic pressure but the total pulmonary and systemic resistance were lowered. Case 7 had 2:1 atrioventricular block throughout the period of measurement. None of the parameters was significantly altered. Case 8 showed a slight

TABLE 3 *Group I—acute myocardial infarction: (b) Haemodynamic effects of continuous infusion of glucagon (20 mg./24 hr.) for 48 hours*

Time	*HR/ min.*	*CO (l./min.)*	*SV (ml./beat)*	*AP (mm. Hg)*	*PAP (mm. Hg)*	*Mean AP (mm. Hg)*	*Mean PAP (mm. Hg)*	*TSR (dynes/sec./cm.$^{-5}$)*	*TPR (dynes/sec./cm.$^{-5}$)*	*ECG*
Case 6										
Control	75	3·0	40	107/55	26/13	73	17	1935	453	Sinus rhythm
24 hr.	86	2·5	29	101/56	25/15	71	18	2315	594	Atrial fib.
48 hr.	77	3·5	45	106/55	22/10	72	14	1639	311	Sinus rhythm
Case 7										
Control	48	2·9	60	146/44	36/10	78	18	2162	506	2:1 AV block
24 hr.	50	2·8	56	122/39	27/10	67	16	1907	455	2:1 block
48 hr.	54	2·7	50	125/48	31/11	74	18	2188	534	2:1 block
Case 8										
Control	77	3·6	47	164/80	29/14	108	19	2370	415	Sinus rhythm
24 hr.	75	3·6	49	150/67	23/10	95	15	2080	318	Sinus rhythm
48 hr.	80	3·3	42	157/72	24/10	100	15	2406	349	Sinus rhythm

HR, heart rate; CO, cardiac output; SV, stroke volume; AP, systemic arterial pressure; PAP, pulmonary arterial pressure; TSR, total systemic resistance; TPR, total pulmonary resistance.

fall in cardiac output at 48 hours with diminished stroke volume and a fall in total pulmonary resistance. No side-effects were noted.

Comment

The single dose method confirms that glucagon 2–5 mg. given intravenously increases the stroke volume in acute myocardial infarction. Its positive chronotropic effect also contributes to an increase in the cardiac output. The improved cardiac performance may explain the lower pulmonary arterial pressure and total pulmonary vascular resistance. The systemic pressure is raised and total systemic resistance is lowered, possibly due to decreasing sympathetic release associated with the better performance of the heart. The maximum haemodynamic effects occur within 10 minutes after administration of the drug and may last for at least half an hour. Further observations with continuous infusion of various dosages of glucagon are required to determine if the drug can maintain an increased cardiac output. Booster doses of 2–5 mg. glucagon at half-hourly intervals over a critical period may be the method of choice to obtain maximum benefit from the positive inotropic action of the drug.

Group 2: chronic rheumatic heart disease

The 11 patients studied were undergoing routine cardiac catheterization with a view to possible operation. The clinical diagnoses are shown in Table 4: 9 had mitral stenosis and 2 had aortic insufficiency as the dominant valve lesions. The dose of glucagon used in each patient was 2 mg. administered directly into the pulmonary artery over a period of 1 minute. Catheters were placed in the pulmonary artery, ascending aorta, and also in the left side of the heart in 7 patients, using the transseptal approach with a modified Brockenbrough needle or by the retrograde approach to the left ventricle through the femoral artery. A Cournand needle was placed in a brachial artery and cardiac output measured after injecting 2·5 mg. indocyanine green dye into the pulmonary artery with brachial artery withdrawal through a Gilford densitometer coupled to a Sanborn photographic recorder. All pressures were measured with Sanborn transducers with the reference point 5 cm. below the sternal angle, with simultaneous electrocardiographic recordings. Pulmonary arterial blood samples were taken at selected intervals for blood sugar estimations with the Technicon Autoanalyser, and serum aspartate transaminase and lactic dehydrogenase activity was measured. Left ventricular contractility was calculated where data permitted and expressed as maximum left ventricular dp/dt or pressure-time index (Sarnoff *et al.*, 1958; Sonnenblick *et al.*, 1965). After control measurements had been taken, the glucagon was injected, and measurements were repeated at intervals of 2, 5, 10, 20, and 30 minutes. The absolute values of the parameters are shown in Table 4, and the percentage changes from control values in Tables 5 and 6.

Results in Group 2

Cardiac output (Tables 4, 5, and 6) The cardiac output was increased in 10 patients at some time during the 30-minute period after the injection of glucagon (Table 4, Cases 10–19). The average increase for the group as a whole at the 5-minute interval was 26·1 per cent (Table 5). The maximum increase usually occurred within the first 10 minutes (Table 6).

Stroke volume (Tables 4 and 5) The stroke volume was increased in all the patients who had an increased cardiac output (Table 4), and the average increase in stroke volume at the 10-minute interval was statistically significant ($p < 0.05$, Table 5).

Heart rate (Table 5) The ventricular rate was increased in all cases, the maximum average increase after 2 minutes being 19 per cent.

Left ventricular contractility (Tables 4, 5, and 6) The maximum left ventricular dp/dt was calculated in 6 patients, and the pressure-time index in 3 patients (Table 4). These parameters showed an increase with maximum values during the first 10 minutes (Table 6), the greatest average percentage change being after 2 minutes, 20·8 per cent (Table 5).

Total systemic resistance (Tables 4 and 5) Total systemic resistance was measured in 6 patients (Table 4). From the limited data available it tended to be reduced during the 20 minutes after the injection of glucagon. The maximum average reduction was 22·3 per cent at 5 minutes (Tables 4 and 5, Cases 10, 13, 15, and 18).

Mitral valve gradient (Fig. 1). In 1 patient (Table 4, Case 9) who had mitral restenosis following a previous mitral valvotomy, it was possible to place catheters on either side of the mitral valve connected to equisensitive transducers. There was an increase in the end-diastolic mitral value gradient from 19 mm. Hg to 25 mm. Hg after glucagon injection (Fig. 1).

Blood sugar (Table 5) Blood sugar levels were increased, the average control value being 106 mg./100 ml. Between 50 and 60 minutes after injection of glucagon the blood sugar levels remained elevated by 47·9 per cent.

TABLE 4 *Croup 2: Chronic rheumatic heart disease: haemodynamic changes produced by injection of 2 mg. glucagon into pulmonary artery in patients with rheumatic heart disease*

Case No.	*Age (yr.)*	*Clinical diagnosis*	*Time after glucagon given (min.)*	*Cardiac output (l./min.)*	*Heart rate (beats/min.)*	*Stroke volume (ml./beat)*	*Left ventricular contractility*		*Total systemic resistance (dynes/sec./cm.$^{-5}$)*
							Max. LV dp/dt (mm. Hg/sec.)	*Pressure-time index (mm. Hg/sec./min.)*	
9	30	Mitral restenosis	Control		82		1755		
			2		111		2300		
			5		100		2031		
			10		92		1629		
			20		95		—		
			30		89		1623		
10	52	Mitral stenosis	Control	1·57	96	16·3			3415
			2	2·23	100	22·3			2724
			5	3·30	90	36·6			1794
			10	—	99				
			20	2·89	92	31·4			1994
			30		106				
11	37	Aortic insufficiency	Control	4·32	64	68·0	1274		
			2	6·69	67	99·9	2028		
			5	6·03	62	97·2	1867		
			10	6·18	65	95·1	1677		
			20				1888		
			30	5·15	64	80·5	1390		
12	37	Aortic insufficiency	Control	8·06	90	89·6		1996	624
			2	7·83	97	80·7		1939	755
			10	7·82	101	77·4		2100	
			20	8·64	94	91·9			592
			30		88			1785	
13	24	Mitral stenosis	Control	6·00	70	86·3		2043	1160
			2	8·45	98	86·2		2736	852
			5	7·93	79	100·4		2672	927
			10	6·38	71	89·9		2192	1087
			20	5·94	69	86·0		2363	1212
			30	5·68	71	80·0		1929	1041
14	40	Mitral stenosis	Control	4·65	79	58·8	2265	1889	1376
			2	4·52	103	43·9	2717		1451
			5	4·82	93	48·7	2960		
			10	4·77	81	58·9	2645	1893	1374
			20	3·89	77	50·6	2198	1803	1724
			30				2075	1794	
15	45	Mitral stenosis; pulmonary hypertension	Control	2·53	88	28·9			2369
			2	2·50	99	25·2			
			5	2·96	79	37·5			1998
			10	2·41	85	28·3			2389
			20	2·62	78	33·7			2132
			30	1·75	85	20·6			3387
16	46	Mitral stenosis	Control	4·54	66	69·3	2138		
			2	5·02	78	64·4	2303		
			5	4·51	63	71·6	1999		
			10	4·56	58	78·6	1695		
			20	5·08	60	84·7	1970		
			30	3·92	61	64·2	1765		
17	36	Mitral stenosis	Control	5·13	81	63·4	1825		1059
			2	6·19	84	73·6	2008		
			5	5·87	77	76·2	1884		
			10	5·36	78	68·8			
			20	4·69	74	63·4			
			30	4·60	76	60·5			
18	61	Mitral stenosis	Control	2·03	101	20·4			4877
			2	2·09	120	17·4			5131
			5	2·09	114	18·4			4584
			10	2·27	99	22·9			4366
			20	2·34	108	21·7			4305
			30	2·18	115	18·9			4336
19	42	Mitral stenosis; pulmonary hypertension	Control	2·23	81	27·4	1788		3297
			2	2·86	84	34·1	2093		
			5	2·57	72	35·7	1800		
			10	2·33	70	33·3	1810		
			20	1·73	69	25·0	1840		
			30	2·30	81	28·4	1930		

TABLE 5 *Group 2: chronic rheumatic heart disease: haemodynamic effects of injecting glucagon, 2 mg., into pulmonary artery in 11 subjects expressed as average changes per cent*

Parameter measured	*Mean per cent change* (Δ%) (± *SEM*)					
	Minutes after glucagon injection					
	2	5	10	20	30	
Cardiac output	+19·3* (±6·7)	26·1* (±11·3)	+8·6 (±5·2)	+7·7 (±10·2)	+3·8 (±6·1)	
Heart rate	+19·0* (±6·1)	+3·5 (±3·8)	−2·1 (±2·0)	−2·6 (±2·9)	+1·6 (±2·3)	
Stroke volume	+7·4 (±7·5)	+26·7 (±13·8)	+12·2* (±4·8)	+13·0 (±10·6)	−4·8 (±5·3)	
Total systemic resistance	+3·0 (±8·9)	−22·3 (±8·9)	−4·0 (±2·7)	−6·4 (±9·0)	—	
Left ventricular contractility (either max. LV dp/dt or pressure-time index)	+20·8* (±5·4)	+16·5 (±7·3)	+5·5 (±6·1)	+8·0 (±8·6)	−3·7 (±4·2)	
						50–60 min. (n=4)
Blood sugar	—	+28·0* (±5·4)	+40·7* (±4·0)	+73·7* (±6·4)	+80·9* (±6·7)	+47·9* (±11·1)

SEM, Standard error of mean.
* $p < 0.05$.

TABLE 6 *Group 2: chronic rheumatic heart disease: haemodynamic effects of injecting glucagon, 2 mg., into pulmonary artery; percentage change in cardiac output and left ventricular contractility in 11 subjects*

Case No.	*Age (yr.)*	*Diagnosis*	*Parameter*	*Minutes after glucagon IV*				
				2	5	10	20	30
9	30	Mitral restenosis	Left ventricular contractility (Δ%)	+31·1	+15·7	—	—	—
10	52	Low output mitral stenosis	Cardiac output (Δ%)	+41·1	+108·9	—	+82·9	—
11	37	Minimal aortic insufficiency	Cardiac output (Δ%); left ventricular contractility (Δ%)*	+54·9 +59·2	±39·6 +46·5	+43·1 +36·6	— +48·2	+19·2 +9·1
12	37	Minimal aortic insufficiency	Cardiac output (Δ%); left ventricular contractility (Δ%)	−2·9 −2·9	— —	−3·0 +5·2	+7·2 —	— −10·5
13	24	Minimal mitral stenosis	Cardiac output (Δ%); left ventricular contractility (Δ%)	+40·8 +30·3	+32·2 +27·2	+6·3 +4·4	−1·0 +12·5	−5·3 −8·1
14	40	Minimal mitral stenosis	Cardiac output (Δ%); left ventricular contractility (Δ%)	−2·8 +16·6	+3·7 +30·7	+2·6 +8·5	−16·3 −3·8	— −6·7
15	45	Pulmonary hypertensive mitral stenosis	Cardiac output (Δ%)	−1·2	+18·2	−4·7	+3·6	−30·8
16	46	Minimal mitral stenosis	Cardiac output (Δ%); left ventricular contractility (Δ%)	+10·6 +7·7	−0·7 −6·5	+0·4 −20·7	+11·9 −7·9	−13·7 −17·4
17	36	Mild mitral stenosis	Cardiac output (Δ%); left ventricular contractility (Δ%)	+20·7 +10·0	+14·4 +1·0	+4·5 —	−8·6 —	−10·3 —
18	61	Mitral stenosis and pulmonary disease	Cardiac output (Δ%)	+3·0	+3·0	+11·8	+12·3	+4·4
19	42	Pulmonary hypertensive mitral stenosis	Cardiac output (Δ%); left ventricular contractility (Δ%)	+28·3 +17·1	+15·2 +0·7	+4·5 +1·2	−22·4 +2·9	+3·1 +7·9

* Either maximum left ventricular dp/dt or pressure-time index.

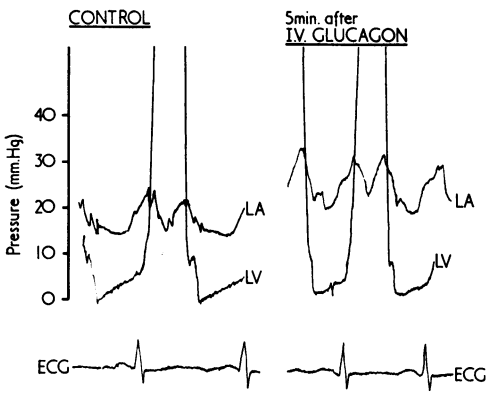

FIG 1 *Increase in mitral valve gradient in mitral restenosis after 2 mg. glucagon into pulmonary artery. LA, left atrial pressure; LV, left ventricular pressure. End-diastolic mitral value gradient increased from 19 to 25 mm. Hg.*

Serum enzymes Serum aspartate transaminase and lactic dehydrogenase levels remained within normal limits for up to one hour after the injection of glucagon.

Side-effects Seven patients felt slight nausea shortly after completion of the glucagon injection. No vomiting occurred. Three patients complained of palpitations due to increased heart rate. No arrhythmias occurred. A sensation of warmth was experienced by two patients.

Comments Glucagon increased the cardiac output immediately after injection by increasing the contractility of the myocardium and the heart rate. With the dosage used its maximum effect on cardiac performance took place within 10 minutes and lasted up to 30 minutes.

Group 3: peripheral vascular effects Forearm blood flow and calf blood flow were measured by venous occlusion plethysmography (Greenfield, Whitney, and Mowbray, 1963).

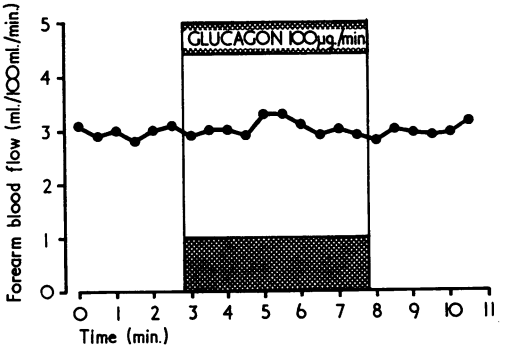

FIG 2 *The average response of forearm blood flow in four patients to the infusion of glucagon, 100 µg./min., into the corresponding brachial artery. Glucagon was infused during the period between the vertical lines.*

Forearm blood flow

Seven patients were studied. A Cournand needle was placed in the brachial artery and normal saline was infused at the rate of 4 ml./min. throughout the period of observation.

No significant changes in blood flow were noted after intra-arterial injections of 20 µg., 40 µg., 100 µg., and 500 µg. glucagon. The average response of blood flow in four patients to infusion of 100 µg./min. is illustrated in Fig. 2. During the infusion period the forearm blood flow was not significantly altered.

Calf blood flow.

Three patients were studied after intravenous injection of 2 mg. glucagon (Table 7). In two patients (Cases 18 and 20) there was a slight fall in vascular resistance at 8 minutes. In one patient (Case 16) there was no significant change in ventricular systolic pressure or calf blood flow.

Comment

Glucagon does not appear to have any effect on peripheral resistance in the forearm or calf.

TABLE 7 *Calf blood flow and vascular resistance in three patients before and after intravenous injection of 2 mg. glucagon*

Case No.	*Control minute*			*2nd minute*			*4th minute*			*8th minute*			*12th minute*			*20th minute*		
	P	*F*	*R*	*P*	*F*	*R*	*P*	*F*	*R*	*P*	*F*	*R*	*P*	*F*	*R*	*P*	*F*	*R*
20	75	0·7	107	74	0·7	105	74	0·7	105	73	0·8	91	72	0·6	120	70	0·6	116
16	139*	1·3	—	136*	1·7	—	135*	1·1	—	—	—	—	—	—	—	144*	1·0	—
18	128	0·9	142	131	0·7	187	127	1·3	98	126	1·4	90	124	1·0	124	128	0·9	135

* Left ventricular systolic pressure.

P, mean arterial pressure in mm. Hg; F, calf blood flow in ml./100 ml./min.; R, calf vascular resistance in arbitrary units, i.e. P divided by F.

Discussion

Glucagon is believed to activate adenyl cyclase in the myocardium with the release of energy from phosphate bands for enhanced myocardial contractility (Sutherland, Robison, and Butcher, 1968). Increased myocardial contractility has been shown in cases of chronic rheumatic heart disease. It appears to be the essential cardiovascular effect of the hormone, and accounts in part for the increased cardiac output. These observations suggest that the peripheral vascular changes seen after intravenous glucagon are secondary to the central reflexes resulting from the drugs' action on the heart muscle, as plethysmography did not show any increase in muscle blood flow when the drug was given intravenously or infused intra-arterially. The improved cardiac performance may also account for the lowering of pulmonary artery pressure and pulmonary vascular resistance. The systemic pressure is likewise raised by the increased cardiac output, but this is counterbalanced by the fall in systemic resistance presumably due to the release of sympathetic tone with the improved cardiac performance. The positive inotropic effect of the drug seen in most of the patients studied was also shown by the increased stroke volume as the main cause of the augmented cardiac output. A positive chrontropic effect also occurred, and caused a few patients to complain of palpitations, but this was transitory. Increased cardiac output has also been observed in chronic heart disease by other authors (Williams *et al.*, 1969). Greenspan, Edmands, and Fisch (1969) have suggested that the myocardial action is associated with alterations with transmembrane flux of calcium, sodium, and potassium ions, as reflected in changes in transmembrane action potential.

The haemodynamic effects after an intravenous injection of a single dose of glucagon 2–5 mg. are immediate and dramatic. It has been proposed that it might be useful in increasing the cardiac output in congestive heart failure (Brogan, Kozonis, and Overy, 1969). Unlike other positive inotropic agents such as isoprenaline and digitalis, glucagon has the advantage that it does not increase cardiac irritability, and its use does not preclude the use of lignocaine or electrical cardioversion, should the need arise, which is of particular importance in acute myocardial infarction. Though its action is rapid, its haemodynamic effects are short lived, probably due to the extremely rapid destruction of the drug by the liver. This may explain why continuous infusion of the drug in acute myocardial infarction exerted no significant haemodynamic effect, the infusion rate employed being only 0·83 mg. per hour. These results suggest that maximum haemodynamic benefit is likely to be achieved by repeated intravenous doses of 2–5 mg. glucagon at half-hourly intervals. The results in acute myocardial infarction are encouraging and warrant further observations, for example, in cardiogenic shock. Its haemodynamic action in chronic rheumatic heart disease is likely to have less clinical application on account of the short duration of action. It may increase the left atrial pressure in mitral stenosis and thereby precipitate pulmonary oedema. However, it may have a place in the therapy of low output failure following cardiac surgery. Its myocardial stimulant action, short response, and the absence of arrhythmias could make glucagon useful as a provocative agent in the detection of hypertrophic obstructive cardiomyopathy. Finally, in the dosage used in these investigations there were no significant toxic effects. The transient slight nausea was probably due to inhibition of gastro-intestinal motility produced by glucagon (Sporn and Necheles, 1956). Though large doses of glucagon can cause electrocardiographic abnormalities and death in geese due to acute myocardial degeneration (Hoak, Conner, and Warner, 1968), serum enzyme levels in our patients with rheumatic heart disease were not raised, and in the doses used the drug appears to be safe. The glycogenolytic action of glucagon which is confined to the liver caused hyperglycaemia in the patients studied, but maximum blood sugar levels rarely exceeded 200 mg. per 100 ml., and were incidental to the haemodynamic changes.

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